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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,687	06/13/2006	Pasqua Anna Oreste	GRT/3687-177	2203

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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
BLAND, LAYLA D	

ART UNIT	PAPER NUMBER
1623	

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10/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,687	ORESTE ET AL.	
	Examiner	Art Unit	
	LAYLA BLAND	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *1-16 and 28-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

3DETAILED ACTION

This office action is a response to Applicant's amendment and declaration of Pasqua Oreste, submitted March 21, 2008, wherein claims 17 and 22 are amended, and Applicant's response to restriction submitted July 11, 2008.

Applicant's election with traverse of Group I, claims 17-27 in the reply filed on July 11, 2008 is acknowledged. The traversal is on the ground(s) that there is no serious burden on the examiner to prosecute claims 17-27 and 32-35 because all of them were already examined on the merits in the first office action. This is not found persuasive because, as mentioned in the requirement for restriction mailed June 11, 2008, compositions comprising (epi)K5-amine-O-oversulfate compounds were not examined due to an oversight by the examiner. Claims 32-35 were misinterpreted by the examiner as being drawn to epiK5-N,O-sulfate compounds and were examined as such. Thus, compositions comprising (epi)K5-amine-O-oversulfate compounds were not examined.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-16 and 28-31 were withdrawn previously.

Claims 1-16 and 28-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement with respect to claims 32-35 in the reply filed on July 11, 2008.

Claims 17-27 are examined on the merits herein.

In view of Applicant's amendment submitted March 21, 2008, the rejection of claim 17 under 35 USC 112, second paragraph for omitting essential elements, is withdrawn.

In view of Applicant's amendment submitted March 21, 2008, the rejection of claim 22 under 35 USC 112, second paragraph for being indefinite, is withdrawn.

The provisional rejection of Claims 17-27 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Application No. 11/440749 is withdrawn because that application is abandoned.

The provisional rejection of Claims 17-27 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Application No. 10/868,359 is withdrawn because that application is abandoned.

The provisional rejection of Claims 17-27 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Application No. 11/030,156 is withdrawn because that application is abandoned.

In view of Applicant's remarks submitted March 21, 2008, the rejection of claims 17-21, 23-25, and 27 under 35 USC 102(b) as being anticipated by Oreste et al. is modified as follows:

Claim Rejections - 35 USC § 103

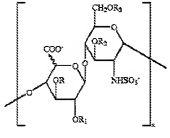
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17-21, 23-25, and 27 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Oreste et al. (WO 02/50125, June 27, 2002, PTO-1449 submitted June 13, 2006).

Oreste et al. teach glycosaminoglycans derived from K5 polysaccharides [see abstract] which consist of a mixture of chains in which at least 90% of said chains have the formula



, wherein 40-60% of the uronic acid units are iduronic acid, the sulfation degree is 2.3 to 2.9, R_3 is 85% to 95% SO_3^-, R_2 is 17-21% SO_3^-, R_1 is about 15-35% SO_3^- in iduronic units and 0-5% SO_3^- in glucuronic units, R is from 20-40% SO_3^- in glucuronic units and 0-5% in iduronic units, and the mean molecular weight is from about 6,000 to about 8,000 [claims 25 and 31]. In one embodiment, n is from 3 to 15 [claim 29]. Oreste et al. also teach pharmaceutical compositions comprising these compounds and pharmaceutically acceptable carriers [claim 38]. The compounds have high antithrombin activity and are useful for the control of coagulation [see abstract].

Oreste et al. are silent on the structure at the reducing end of the majority of the chains. However, the skilled artisan would understand that compounds made by the methods of Oreste et al., wherein the compounds are prepared from a low molecular

weight fraction of K5 [page 15, lines 1-4], or fractionated [page 15, lines 21-24], or depolymerized early in the synthesis [page 14, lines 27-31] would necessarily have the claimed sulfated structure at the reducing end of the majority of the chains. Since the Office does not have the facilities for preparing the claimed materials and comparing them with prior art inventions, the burden is on Applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980).

Claims 17 and 33-25 are product-by process claims. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted). The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.). See MPEP 2113. The limitation "depolymerized" is also interpreted as drawn to the method of production, which results in a low molecular weight product.

Response to Arguments

Applicant argues that, although WO 02/50125 discloses a series of processes for preparing depolymerized products, only depolymerization at the end of the process is specifically described. As was mentioned above, Oreste et al. are silent on the structure at the reducing end of the majority of the chains in the structures in claims 25 and 31 and process steps are not included in the claims. Several processes for preparing the compounds are disclosed; processes wherein the product is depolymerized at the end of the process would not result in the instantly claimed compounds, but processes wherein the compounds are prepared from a low molecular weight fraction of K5 [page 15, lines 1-4], or fractionated [page 15, lines 21-24], or depolymerized early in the synthesis [page 14, lines 27-31] would have the claimed sulfated structure at the reducing end of the chains. Thus, the instant claims are either anticipated by (in the case wherein the compounds are prepared from low molecular weight fractions, fractionated, or depolymerized early in the synthesis) or obvious over (in the case wherein the compounds are polymerized last, alternative synthetic strategies are taught) Oreste et al.

The following rejections of record are maintained:

Claims 22 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oreste et al. (WO 02/50125, June 27, 2002, PTO-1449 submitted June 13, 2006) in view of Naggi et al. (Carbohydrate Research 336 (2001) 283-290, PTO-1449 submitted June 13, 2006).

Oreste et al. teach as set forth above.

Oreste et al. do not teach derivatives having a content of 45-55% in glucosamine 3-O-sulfate.

Naggi et al. teach that sulfation at C-3 of central $GlcNSO_3$ residue increases the aXa activity of heparin [page 288, first paragraph]. Naggi et al. also teach desulfation kinetics of sulfated heparin in DMSO-MeOH at different times and temperatures, and show that derivatives with 45-60% glucosamine 3-O-sulfate can be obtained at 65°C-90°C, for 30-90 minutes [page 286, Table 1].

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare compounds similar to those taught by Oreste et al., having 45-55% of glucosamine 3-O-sulfate. The skilled artisan would have been motivated to do so in order to enhance the activity of the compounds taught by Oreste et al. Naggi et al. teach that sulfation at C-3 of the central $GlcNSO_3$ residue increases the aXa activity of heparin and teach conditions for selective desulfation of supersulfated low-molecular weight heparin. The compounds of Oreste et al. are structurally similar to heparin and function similarly, so the skilled artisan could extend the teachings of Naggi et al. to the teachings of Oreste et al. with a reasonable expectation of success.

Response to Arguments

Applicant argues that the instantly claimed products have unexpected properties, and presents the declaration of Pasqua Oreste in support. Ms. Oreste presents data for the comparison of inventive compound Example 1 with prior art compound Example 2. MPEP 2145 states: "If a *prima facie* case of obviousness is established, the burden

shifts to the applicant to come forward with arguments and/or evicence to rebut the *prima facie* case," and "the evidence must be reasonably commensurate in scope with the claimed invention." The compound of Example 1 has a sulfation degree of 2.83 and a content of 95-100% in N-sulfated glucosamine, 80% in 6-O-sulfated glucosamine, 50% in 3-o-sulfated glucosamine, 40% in 3-O-sulfated glucuronic acid and 20% in 2-O-sulfated iduronic acid. Claims 17-21, 23-24, and 27 are drawn to a broad genus of compounds, of which Example 1 is a member, but Example 1 is not representative of the broad genus. For example, Example 1 has a sulfation degree of 2.83, at one end of the range 2.3-2.9 recited in claim 17. Example 1 is also drawn to products having specific content in N-sulfated glucosamine, 3-O-sulfated glucosamine, 3-O-sulfated glucuronic acid and in 2-O-sulfated iduronic acid, and claim 17 is not limited at all in those respects. In comparing Example 1 with Example 2, there are numerous points of difference between them, as was pointed out by Applicant on page 18 of the response dated March 21, 2008. Thus, it is difficult to determine which differences were instrumental in producing the properties shown in Table 3 of the declaration of Pasqua Oreste submitted March 21, 2008. It is also unclear whether the data shown for Example 2 was obtained under the same conditions as the data for Example 1.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 17-27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 35-62 of copending Application No. 09/950,003. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in each application are drawn to substantially overlapping genera of compounds and pharmaceutical compositions comprising such. The claims of copending Application No. 09/950,003 do not require a specific structure at the reducing end of the majority of the chains, but this is an inherent feature of the compounds due to the method of their production.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicant will address the double patenting rejection when the claims are otherwise allowable.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAYLA BLAND whose telephone number is (571)272-9572. The examiner can normally be reached on Tuesday - Friday, 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner, Art Unit 1623

/Layla Bland/
Examiner, Art Unit 1623